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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/785,374	02/24/2004	Marshall L. Summar	1242/58	1629

25297 7590 03/02/2010

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EXAMINER	
JOHANNSEN, DIANA B	
ART UNIT	PAPER NUMBER
1634	
MAIL DATE	DELIVERY MODE
03/02/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/785,374	SUMMAR ET AL.	
	Examiner	Art Unit	
	Diana B. Johannsen	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-6,8-10,19-23,26-29,34-36 and 38-42* is/are pending in the application.

4a) Of the above claim(s) *6,34,36 and 41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,5,8-10,19-23,26-29,35,38-40 and 42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1108;0109;1209*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

FINAL ACTION

1. This action is responsive to the Response to Restriction/Election Requirement filed August 17, 2009, as well as the Response filed November 17, 2009 (including a summary of the content of the interview conducted May 28, 2009, and reiterating the response to restriction requirement of August 17, 2009). The response to restriction/election is addressed below. The summary of the interview has been reviewed and is considered complete and accurate. Claims 6, 34, 36, and 41 are withdrawn (see below) and claims 1-2, 4-5, 8-10, 19, 21-23, 26, 28-29, 35, 38-40, and 42 are under consideration herein (with claims 19 and 21-23 being under consideration to the extent that those claims depend from claim 35).

2. Applicant's amendments and arguments have been thoroughly reviewed, but are moot in view of the new grounds of rejection set forth below, which new grounds were necessitated by applicant's amendments. Any rejections and/or objections not reiterated in this action have been withdrawn. **This action is FINAL.**

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restriction

4. Applicant's election without traverse of the species of pulmonary hypertension in the reply filed on August 17, 2009 (and reiterated November 17, 2009) is acknowledged. The examiner concurs that claims 1, 2, 4-5, 8-10, 19, 21-23, 26, 28-29, 35, 38-40, and 42 read on the elected species. Applicant's statements that examination of both the species of pulmonary hypertension and the species of cardiac surgery would

not pose an undue burden are acknowledged. Because the two species of pulmonary hypertension and cardiac surgery have been found to require consideration of different prior art references and to raise different issues under 35 USC 112, first paragraph, the species election remains in effect. However, the examiner concurs that (as was indicated in the Election/Restriction mailed April 15, 2009) applicant will be entitled to consideration of additional species upon allowance of a generic claim, and further that, upon determining that a species is allowable, examination will be extended in accordance with the guidance given in MPEP 803.02. .

5. Claims 6, 34, 36, and 41 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on August 17, 2009. It is also again noted that the species election was first imposed in the Election/Restriction of September 25, 2006 (see paragraph 2 of the Election/Restriction mailed April 15, 2009).

Claim Rejections - 35 USC § 112, first paragraph

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

THE FOLLOWING ARE NEW GROUNDS OF REJECTION NECESSITATED BY APPLICANTS' AMENDMENTS:

7. Claims 1-2, 4-5, 8-10, 19, 21-23, 26, 28-29, 35, 38-40, and 42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the

specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection**.

In the amendment of January 26, 2009, applicant amended the claims to require a subject "under conditions of suboptimal urea cycle function" that "further comprises decreased plasma citrulline" (see claim 1 and claims dependent therefrom, of which claim 5 recites the elected disorder of "pulmonary hypertension"), a subject having a disorder or "about to be exposed to" an environmental stimulus "associated with decreased plasma citrulline" (see claim 4 and claims dependent therefrom, including the above-referenced claim 5), a subject suffering from a disorder "associated with decreased plasma citrulline, wherein the disorder is pulmonary hypertension" (claim 35 and claims dependent therefrom), and a subject "under conditions of suboptimal urea cycle function" that "further comprises decreased plasma citrulline" (see claim 38 and claims dependent therefrom). Thus, the claims under consideration embrace both a general type of subject "under conditions of suboptimal urea cycle function" wherein the suboptimal function "further comprises decreased plasma citrulline" and subjects having a disorder referenced in the claims as being "associated with decreased plasma citrulline" wherein the disorder is the elected species of pulmonary hypertension. New dependent claims 39-40 and 42 further require that the "decreased plasma citrulline" of independent claims 1, 35 and 42 "comprises plasma citrulline levels of less than 24.4 uM". However, neither the instant specification nor the specification of any of applicant's claimed parent application provide basis for these new limitations.

The reply of January 26, 2009 points to several areas of the specification as providing basis for the amended claims (each of which is discussed below), and it is noted that the originally filed disclosures of the instant application and of each parent application have also been reviewed by the examiner. At page 46, lines 13-14, the specification states that sub-optimal urea cycle function can "further comprise...decreased citrulline". Page 49, lines 22-24, states that a "significant decrease in urea cycle intermediates (citrulline, arginine) was observed in subjects undergoing BMT". Page 73, lines 23-31 describes measuring plasma citrulline levels in BMT patients before and after chemotherapy, and reports that citrulline levels "fell in virtually all patients" of the subset tested. Page 74, lines 10-23, discloses that "Baseline plasma levels of citrulline...had prognostic importance" in the BMT patients studied. Page 76, line 21 through page 77, line 23 describes a "significant fall in citrulline levels...from patients under going BMT" and again references the "prognostic importance" of plasma citrulline levels in patients undergoing BMT and chemotherapy. Page 79, lines 6-15 (which includes Table 4), again discloses decreases in plasma citrulline in BMT patients following chemotherapy, and further discloses (at lines 16-23) administering citrulline to such patients. Page 91, lines 5-9 and 23-26 discloses assaying infants admitted to the hospital suffering from respiratory distress (some of whom were eventually diagnosed with persistent pulmonary hypertension of the newborn (PPHN)). It is noted that in this example (Example 7), applicants later report that "infants who developed PPHN had significantly lower serum arginine and citrulline levels on amino acid analysis" (page 94, lines 28-29), and that no such differences were

identified in infants with different primary diagnoses (page 95, lines 11-18). Example 7 also includes an additional discussion of serum citrulline levels in the infants studied therein (at page 95, line 19-page 96, line 9). Example 8 (pages 96-97) discloses the administration of intravenous citrulline to piglets and reports the affect of this administration on plasma arginine levels). Original claims 3, 7, 20, and 27 (cited by applicant as providing support for the amended claims) disclose that "the sub-optimal urea cycle function further comprises decreased urea cycle intermediate production" (claim 3) and disclose citrulline as a "nitric oxide precursor" (claims 7, 20 and 27). Thus, the specification includes a general disclosure that suboptimal urea cycle function may further comprise "decreased citrulline." The specification more specifically discloses that decreased levels of plasma citrulline were detected in subjects who received chemotherapy while undergoing BMT and that plasma citrulline levels were of prognostic importance in such patients, and additionally that infants who developed PPHN (in Example 7) were found to have significantly lower serum citrulline levels. However, the specification does not provide basis for the general type of subject of the claims, a subject "under conditions of suboptimal urea cycle function" wherein the suboptimal function "further comprises decreased plasma citrulline;" nor does the specification provide basis for subjects having a disorder referenced in the claims as being "associated with decreased plasma citrulline" wherein the disorder is the elected species of pulmonary hypertension.

Regarding new claims 39-42, the specification further fails to provide basis for these further limitations on the "decreased plasma citrulline levels" as recited in the

claims. Page 73 discloses a decrease from "23.4±1.3 uM to 9.1±0.7 uM ($p<0.05$)" before and after chemotherapy in the BMT patients discussed above, and at page 74, sixty day survivors of BMT are reported to have significantly higher baseline levels of citrulline than nonsurvivors "(24.4±1.3 uM vs. 17.7±2.9 uM)". Similar data are reported in Table 4 (page 79) for BMT patients, in which citrulline levels "Pre Chemo" are reported as "24 ± 3 uM" and levels "Post Chemo." are reported as 8 ± 1 uM". However, there is no apparent basis in the specification for the general disclosure/definition of "decreased plasma citrulline" as comprising levels "of less than 24.4 uM" as required by the claims; rather, the specification provides particular data in which one particular type of patient group has this specific level of citrulline prior to chemotherapy. Accordingly, basis is lacking in the originally filed specification for the invention of new claims 39-42.

In view of the lack of basis for the presently claimed invention in the instant specification and all parent applications, it is noted that the actual filing date of the instant application, February 24, 2004, is now considered the **effective filing date** pertinent to the present claims.

8. Claims 1-2, 4-5, 8-10, 19, 21-23, 26, 28-29, 35, 38-40, and 42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the

enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (A) the breadth of the claims; (B) the nature of the invention; (C) the state of the prior art; (D) the level of one of ordinary skill; (E) the level of predictability in the art; (F) the amount of direction provided by the inventor; (G) the existence of working examples; and (H) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (*MPEP* 2164.01(a)). It is noted that the examiner has considered all of the evidence related to each of these factors, and that those factors, reasons and evidence that have led to a conclusion that enablement is lacking are discussed below (*MPEP* 2164.04).

Claim 1 and claims dependent therefrom are now drawn to a method of "treating or preventing decreased nitric oxide formation resulting from sub-optimal urea cycle function in a subject" comprising steps of "providing a subject under conditions of suboptimal urea cycle function, wherein the sub-optimal urea cycle function further comprises decreased plasma citrulline" and "administering to the subject a therapeutically effective amount of citrulline, whereby treatment or prevention of decreased nitric oxide formation resulting from sub-optimal urea cycle function is accomplished". Claim 35 and claims dependent therefrom are drawn to a method of "treating or preventing decreased nitric oxide formation resulting from sub-optimal urea cycle function in a subject suffering from a disorder associated with decreased plasma citrulline" comprising steps of "providing a subject suffering from a disorder associated with decreased plasma citrulline, wherein the disorder is pulmonary hypertension" and

"administering to the subject a therapeutically effective amount of citrulline, whereby treatment or prevention of decreased nitric oxide formation resulting from sub-optimal urea cycle function is accomplished". Claim 38 and claims dependent therefrom are drawn to a method "of raising a level of a nitric oxide precursor in a subject suffering from suboptimal urea cycle function" comprising steps of "providing a subject under conditions of suboptimal urea cycle function, wherein the sub-optimal urea cycle function further comprises decreased plasma citrulline" and "administering to the subject a therapeutically effective amount of citrulline, whereby the level of a nitric oxide precursor in the subject is raised". It is again noted that the elected species of disorder is pulmonary hypertension.

It is unpredictable as to whether one skilled in the art could use applicant's invention as it is now claimed. Claim 1 and claims dependent therefrom require that "treatment or prevention of decreased nitric oxide formation resulting from sub-optimal urea cycle function" be accomplished by administration of a "therapeutically effective amount of citrulline" to a subject "under conditions of suboptimal urea cycle function, wherein the sub-optimal urea cycle function further comprises decreased plasma citrulline." Claim 35 and claims dependent therefrom require that "treatment or prevention of decreased nitric oxide formation resulting from sub-optimal urea cycle function" be accomplished by administration of a "therapeutically effective amount of citrulline" to a subject "suffering from a disorder associated with decreased plasma citrulline, wherein the disorder is pulmonary hypertension." Claim 38 and claims dependent therefrom require that "the level of a nitric oxide precursor" be raised via

administration of a "therapeutically effective amount of citrulline" in a subject "under conditions of suboptimal urea cycle function, wherein the sub-optimal urea cycle function further comprises decreased plasma citrulline". However, the specification does not exemplify the successful performance of any methods embraced by the amended claims, and does not otherwise provide evidence that such methods could be performed without undue experimentation. As was discussed briefly above, the specification does disclose the detection of significantly decreased plasma citrulline levels in one specific type of subject, human subjects undergoing BMT, and further teaches that decreased levels in such patients were found to be of prognostic importance (see, e.g., page 49, lines 22-24, page 73, lines 23-31, page 74, lines 10-23, page 76, line 21-page 77, line 23, page 79, lines 6-15). The specification also teaches the administration of arginine and/or citrulline so as to reduce BMT related toxicity, but does not actually exemplify taking such steps, or otherwise provide any evidence that such administration is or would be effective in such patients (page 79, lines 16-23). The specification also discloses assaying infants admitted to the hospital suffering from respiratory distress (some of whom were eventually diagnosed with persistent pulmonary hypertension of the newborn (PPHN)) (Example 7, particularly page 91, lines 5-9, 23-26). Applicants report in this example that "infants who developed PPHN had significantly lower serum arginine and citrulline levels on amino acid analysis" (page 94, lines 28-29), and that no such differences were identified in infants with different primary diagnoses, even when those infants had pulmonary hypertension (page 95, lines 11-18). This evidence suggests a relationship between decreased serum citrulline and a

diagnosis of PPHN (rather than the general category of "pulmonary hypertension"). It is further noted that the specification reports possible associations between serum citrulline levels and "the severity of hypoxemia" in the infants studied, but does not report statically significant findings (page 95, lines 20-25), and similarly reports a possible association between CPS1 genotype and PPHN, but no statistically significant association with citrulline levels (page 95, line 26-page 96, line 9). As with the BMT patient population, no exemplification of any type of treatment/prevention (successful or otherwise) is disclosed in the specification with regard to this patient population (pertinent to claims 1 and 35 and claims dependent therefrom), nor does the specification provide any exemplification or evidence of the successful administration of citrulline to any subject "suffering from sub-optimal urea cycle function" and having decreased plasma citrulline to achieve an increase in any nitric oxide precursor (pertinent to claim 38 and claims dependent therefrom). It is noted that Example 8 (pages 96-97) discloses the administration of intravenous citrulline to a small number of healthy piglets (specifically, 5 piglets), and reports a resulting significant increase in serum arginine (as compared to a saline control). However, such healthy subjects are not embraced by the claims, nor does the specification or the prior art establish that such results reflect what might or would occur in the subject types embraced by the claims (see also the discussion of the prior art, below). In summary, the specification provides no evidence of the successful practice of any embodiment of any of the methods embraced by the pending claims.

Lacking guidance from the specification, one skilled in the art may look to the teachings of the prior art for further guidance with regard to enablement of a claimed invention. In the instant case, the previously cited prior art references of Waugh and Kaesemeyer are silent with regard to an association between pulmonary hypertension (or related disorders) and decreased plasma citrulline, and with regard to whether subjects having a disorder with this feature may be effectively treated using citrulline. Boykin et al (which qualifies as prior art under 35 USC 102(a) and 102(e) based on the current effective filing date of the pending claims) disclose that "Plasma levels of L-citrulline....can be determined as a reflection of systemic NO synthesis in a patient" (see entire reference, particularly paragraph 33) and further teach that pulmonary hypertension may be associated with reduced bioactivity of nitric oxide and "endothelial dysfunction" (see, e.g., paragraph 3). However, while Boykin et al disclose screening for plasma citrulline levels as one indicator of "endothelial dysfunction" (which may include the condition of pulmonary hypertension, as noted above), citrulline is not among the agents suggested by Boykin et al for use in treating or preventing such a condition (see, e.g., paragraphs 65-68). Additionally, in discussing conflicting results obtained using L-arginine therapy in patients with different types of pulmonary hypertension and other related conditions, Aschner (Pediatric Pulmonology Suppl 26:132-135 [October 2004]; cited in the IDS of 01/28/2009) teaches that "well controlled clinical studies are lacking" regarding the use of oral arginine in therapy, and further that "the rapid degradation of oral arginine ...limits its clinical use" (page 133). Aschner further teaches that oral citrulline was disclosed by applicant and co-authors in 2002 as

being "more effective than oral arginine in increasing circulating levels of L-arginine in healthy subjects;" however, Aschner teaches that "More work is needed to determine whether oral citrulline will prove more effective than arginine in raising NO levels and reducing pulmonary vascular resistance in patients with PH" (page 133, right column), and Aschner is also silent with regard to the condition of "decreased plasma citrulline" in subjects or the successful treatment of such subjects, as is required of the present claims. Thus, the Aschner reference, which was published later in the same year of applicant's effective filing date, suggests that the potential effectiveness of citrulline therapy in treating or preventing pulmonary hypertension and/or related conditions exhibiting "decreased plasma citrulline" was unknown and unpredictable at the time the instant invention was made. Thus, in the instant case, the teachings of the prior art cannot be relied upon in providing further enabling guidance with regard to the invention now claimed. Given the high level of skill of one skilled in the relevant art, it is clearly within the ability of such an artisan to conduct further experimentation aimed at determining, e.g., what embodiments (if any) embraced by the claims might be enabled. However, the claims as written requiring the actual treatment/prevention of a condition in a subject exhibiting decreased plasma citrulline (claims 1 and 35 and dependent claims) or the actual increase of a nitric oxide precursor in such a subject (claim 38 and dependent claims), and the possible outcome of such experimentation is entirely unknown and unpredictable. Given the lacking of guidance, evidence and predictability in the specification and in the prior art, it is possible that even an infinite quantity of experimentation would fail to enable even a single embodiment or a limited number of

embodiments embraced by the claims. As such a type and quantity of experimentation is clearly undue, enablement is lacking with regard to the invention presently claimed.

Terminal Disclaimer

9. The terminal disclaimer filed on January 26, 2009 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of any patent granted on application number 12/122,117 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Conclusion

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is

571/272-0744. The examiner can normally be reached on Monday-Friday, 8:30 am-2:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached at 571/272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Diana B. Johannsen/
Primary Examiner, Art Unit 1634